

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. - 48. (Cancelled).

49. (Currently amended) An ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent comprising:

a polypeptide comprising a ~~eye~~ie disulfide-linked peptide having the amino acid sequence

Cys-X₂-X₃-Tyr-X₅-X₆-Cys (SEQ ID NO: 2 71), wherein:

| _____ |

X₂ is Ala, Glu, Phe, Gly, Ile, Lys, Leu, Met, Arg, Thr, Val, Tyr, Asn, Asp, Gln, His, Ser, or Trp;

X₃ is Ser, Phe, Ala, or Tyr;

X₅ is Gly, Ala or DAla; and

X₆ is Thr, Val or Ser,

~~wherein said fibrin-binding polypeptide has the ability to bind fibrin;~~ wherein said polypeptide is conjugated, optionally through a linker, to a paramagnetic metal MR chelate, and wherein said MR imaging agent is capable of binding fibrin.

50. (Currently amended) The ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 49, wherein the amino acid residue X₅ is Gly and the amino acid residue X₆ is Thr.

51. (Currently amended) The ~~isolated, non-naturally-occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 49, wherein said ~~eyelie~~ polypeptide comprises the amino acid sequence

X₁-X₂-Cys-X₄-X₅-Tyr-X₇-X₈-Cys-X₁₀-X₁₁ (SEQ ID NO: ~~47~~ 70), wherein
| _____ |

X₁ is Arg, Asp, His, Leu, or Phe;

X₂ is Ala, Asp, Gly, Pro or Ser;

X₄ is Ala, Glu, Phe, Gly, Ile, Lys, Leu, Met, Arg, Thr, Val, Tyr, Asn, Asp, Gln, His, Ser, or Trp;

X₅ is Ser, Phe, Ala, or Tyr;

X₇ is Gly, Ala or DAla;

X₈ is Thr, Val or Ser;

X₁₀ is His, Leu or Phe; and

X₁₁ is Arg, Asp or His.

52. (Currently amended) An ~~isolated, non-naturally-occurring fibrin-binding polypeptide~~ MR imaging agent comprising:

a polypeptide comprising a ~~eyelie~~ disulfide-linked peptide having the amino acid sequence

Cys-Tyr-X₃-Ser-Tyr-X₆-X₇-X₈-X₉-Cys (SEQ ID NO: ~~47~~ 86), wherein
| _____ |

X₃ is Asn or Asp;

X₆ is Gly or Tyr;

X₇ is His or Val;

X₈ is Pro or Trp; and

X₉ is Trp or Tyr;

~~wherein said fibrin binding polypeptide has the ability to bind fibrin; wherein said polypeptide is~~
conjugated, optionally through a linker, to a paramagnetic metal MR chelate, and wherein said
MR chelate is capable of binding fibrin.

53. (Currently amended) The ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR
imaging agent according to claim 52, wherein the polypeptide comprises ~~comprising~~ the amino
acid sequence

X₁-X₂-X₃-Cys-Tyr-X₆-Ser-Tyr-X₉-X₁₀-X₁₁-X₁₂-Cys-X₁₄-X₁₅-X₁₆ (SEQ ID NO: ~~65~~ 134),
|_____|

X₁ is Asn or Arg;

X₂ is His or Phe;

X₃ is Gly or Leu;

X₆ is Asn or Asp;

X₉ is Gly or Tyr;

X₁₀ is Val or His;

X₁₁ is Pro or Trp;

X₁₂ is Tyr or Trp;

X₁₄ is Asp or Ser;

X₁₅ is Tyr or His; and

X₁₆ is Ser or His.

54. (Currently amended) An ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR
imaging agent comprising:

a polypeptide comprising a ~~eyelie~~ disulfide-linked peptide having the amino acid
sequence

Cys-Pro-Tyr-X_{aa}-Leu-Cys (SEQ ID NO: ~~20~~ 89), wherein
|_____|

X_{aa} is Asp, Gly or Ala, and ~~wherein said fibrin binding polypeptide has the ability to bind fibrin;~~
wherein said polypeptide is conjugated, optionally through a linker, to a paramagnetic metal MR
chelate, and wherein said MR imaging agent is capable of binding fibrin.

55. (Currently amended) The ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR
imaging agent according to claim 54, wherein said ~~eyelie~~ polypeptide has comprises the amino
acid sequence

X₁-X₂-Cys-Pro-Tyr-X₆-Leu-Cys-X₉-X₁₀-X₁₁ (SEQ ID NO:~~66~~ 135), wherein
| _____ |

X₁ is Trp, Phe, His or Tyr;

X₂ is His, Asp or Glu;

X₆ is Asp, Gly or Ala;

X₉ is His, Phe, Tyr or Trp;

X₁₀ is Ile, Leu, or Val; and

X₁₁ is Asn, Gln, Ile, Leu or Val.

56. (Currently amended) The ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR
imaging agent according to claim 49, said ~~eyelie~~ polypeptide having comprising an amino acid
sequence selected from the group consisting of:

Arg-Ser-Cys-Asn-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~5~~ 74);
| _____ |

His-Asp-Cys-Gln-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~6~~ 75);
| _____ |

Phe-Ala-Cys-His-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~7~~ 76);
| _____ |

Arg-Pro-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Phe-Asp (SEQ ID NO:~~8~~ 77);
| _____ |

Leu-Pro-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Leu-Asp (SEQ ID NO:~~9~~ 78);
| _____ |

Phe-Ser-Cys-Trp-Tyr-Ser-Leu-His-Cys-His-Arg (SEQ ID NO:~~10~~ 79);

|_____|

Asp-Pro-Cys-Ser-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~11~~ 80);

|_____|

Leu-Pro-Cys-Ser-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~12~~ 81);

|_____|

Leu-Ser-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Leu-Arg (SEQ ID NO:~~13~~ 82);

|_____|

Leu-Ala-Cys-His-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~14~~ 83);

|_____|

Asp-Gly-Cys-His-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~15~~ 84);

|_____|

Arg-Pro-Cys-Asn-Tyr-Tyr-Gly-Thr-Cys-Leu-His (SEQ ID NO:~~16~~ 85);

|_____|

Pro-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Leu (SEQ ID NO:~~32~~ 101);

|_____|

Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Leu (SEQ ID NO:~~33~~ 102);

|_____|

Cys-Asp-Tyr-Tyr-Gly-Thr-Cys (SEQ ID NO:~~34~~ 103);

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-DAla-Thr-Cys-Leu-Asp (SEQ ID NO:~~40~~ 109);

|_____|

Leu-Ala-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Leu-Asp (SEQ ID NO:~~41~~ 110);

|_____|

Leu-Pro-Cys-Ala-Tyr-Tyr-Gly-Thr-Cys-Leu-Asp (SEQ ID NO:~~42~~ 111);

|_____|

Leu-Pro-Cys-Asp-Ala-Tyr-Gly-Thr-Cys-Leu-Asp (SEQ ID NO:~~43~~ 112);

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-Ala-Thr-Cys-Leu-Asp (SEQ ID NO:~~45~~ 114);

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-Gly-Ala-Cys-Leu-Asp (SEQ ID NO:46-115);

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-Gly-Thr-Cys-Ala-Asp (SEQ ID NO:47 116);

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-Gly-Ser-Cys-Leu-Asp (SEQ ID NO:48 117); and

|_____|

Leu-Pro-Cys-Asp-Tyr-Tyr-Gly-Val-Cys-Ala-Asp (SEQ ID NO:51 120).

|_____|

57. (Currently amended) The ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR imaging agent according to claim 54, said ~~eye~~ polypeptide having comprising an amino acid sequence selected from the group consisting of:

Trp-Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:21 90);

|_____|

Gln-Trp-Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile-Gln (SEQ ID NO:22 91);

|_____|

Gly-Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:23 92);

|_____|

Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:24 93);

|_____|

His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:25 94);

|_____|

Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile (SEQ ID NO:26 95);

|_____|

Trp-Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile-Gln (SEQ ID NO:27 96);

|_____|

Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile-Gln (SEQ ID NO:28 97);

|_____|

Trp-Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile (SEQ ID NO:~~29~~ 98);

|_____|

Gly-Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:~~57~~ 126);

|_____|

Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:~~58~~ 127);

|_____|

His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile-Leu (SEQ ID NO:~~59~~ 128);

|_____|

Phe-His-Cys-Pro-Tyr-Asp-Leu-Cys-His-Ile (SEQ ID NO:~~60~~ 129);

|_____|

Trp-Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile-Gln (SEQ ID NO:~~61~~ 130);

|_____|

Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile-Gln (SEQ ID NO:~~62~~ 131); and

|_____|

Trp-Glu-Cys-Pro-Tyr-Gly-Leu-Cys-Trp-Ile (SEQ ID NO:~~63~~ 132).

|_____|

58. (Currently amended) The ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR imaging agent according to claim 52, said ~~eye~~eye ~~polypeptide having comprising~~ polypeptide comprising an amino acid sequence selected from the group consisting of:

Asn-His-Gly-Cys-Tyr-Asn-Ser-Tyr-Gly-Val-Pro-Tyr-Cys-Asp-Tyr-Ser (SEQ ID NO:~~48~~ 87);

|_____|

and

Arg-Phe-Leu-Cys-Tyr-Asp-Ser-Tyr-Tyr-His-Thp-Trp-Cys-Ser-His-His (SEQ ID NO:~~49~~ 88).

|_____|

59. (Currently amended) An ~~isolated, non-naturally occurring fibrin binding polypeptide~~ MR imaging agent according to any one of claims 49 to 58, wherein said ~~polypeptide~~ polypeptide MR imaging agent selectively binds fibrin ~~but not as compared to~~ as compared to fibrinogen.

60. (Currently amended) An ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 59, wherein said ~~polypeptide~~ MR imaging agent has a K_d for fibrinogen which is at least 1.5 greater than its K_d for fibrin.

61. (Currently amended) An ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 60, wherein said ~~polypeptide~~ MR imaging agent has a K_d for fibrinogen which is at least 10 greater than its K_d for fibrin.

62. (Currently amended) An ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 61, wherein said ~~polypeptide~~ MR imaging agent has a K_d for fibrinogen which is at least 100 greater than its K_d for fibrin.

63. (Currently amended) An ~~isolated, non-naturally occurring fibrin-binding polypeptide~~ MR imaging agent according to claim 62, wherein said ~~polypeptide~~ MR imaging agent has a K_d for fibrinogen which is at least 1000 greater than its K_d for fibrin.

64. (Cancelled).

65. (New) The MR imaging agent according to any of claims 49-58, wherein said paramagnetic metal MR chelate is selected from DTPA and derivatives thereof, DOTA and derivatives thereof, EDTA, TETA, EHPG and derivatives thereof, benzo-DTPA and derivatives thereof, HBED and derivatives thereof, benzo-DOTA, dibenzo-DOTA, NOTA, benzo-NOTA, benzo-TETA, benzo-DOTMA, DOTMA, benzo-TETMA, TETMA, PDTA and derivative thereof, TTHA and derivatives thereof, LICAM and derivatives thereof, and MECAM and derivatives thereof.

66. (New) The MR imaging agent according to claim 65, wherein said paramagnetic metal MR chelate is DOTA.

67. (New) The MR imaging agent according to claim 65, wherein said paramagnetic metal MR chelate is DTPA.

68. (New) The MR imaging agent according to any of claims 49-58, wherein said paramagnetic metal has an atomic number of 21-29, 42, 44, or 57-83.

69. (New) The MR imaging agent according to claim 68, wherein said paramagnetic metal is selected from the group consisting of Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III), Ho(III), Er(III), and Eu(III).

70. (New) The MR imaging agent according to claim 69, wherein said paramagnetic metal is Gd(III).

71. (New) The MR imaging agent according to any one of claims 49-58, wherein said polypeptide is conjugated through a linker to said paramagnetic metal MR chelate.

72. (New) The MR imaging agent according to claim 71, wherein said linker comprises one or more of the following moieties: amide, urea, acetal, ketal, double ester, carbonyl, carbamate, thiourea, sulfone, thioester, ester, ether, disulfide, lactone, imine, phosphoryl, or phosphodiester moieties; substituted or unsubstituted saturated or unsaturated alkyl chains; linear, branched, or cyclic amino acid chains of a single amino acid or different amino acids; derivatized or underivatized polyethylene glycol, polyoxyethylene, or polyvinylpyridine moieties; substituted or unsubstituted polyamide moieties; derivatized or underivatized polyamine, polyester, polyethylenimine, polyacrylate, poly(vinyl alcohol), polyglycerol, or oligosaccharide moieties;

alternating block copolymers; malonic, succinic, glutaric, adipic and pimelic acid moieties; caproic acid; and diamine and dialcohol moieties.

73. (New) The MR imaging agent according to claim 71, wherein said polypeptide is linked through its N- or C-terminus to said paramagnetic metal MR chelate.

74. (New) The MR imaging agent according to claim 73, wherein said linkage comprises an amide moiety.